MULTIPLE-ARM PEPTIDE COMPOUNDS, METHODS OF MANUFACTURE AND USE IN THERAPY

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MULTIPLE-ARM PEPTIDE COMPOUNDS, METHODS OF MANUFACTURE AND USE IN THERAPY

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention concerns peptide or protein molecules having multiple arms which contain specific sequences, domains or groups which are useful to produce improved cell adhesion, proliferation, migration and spreading, anti-inflammation, healing response, antithrombogenic effect and the like. The methods of synthesis of these molecules are described.

References

Some references of interest (in alphabetical order here) are discussed below and include the following:

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Description of Related Art

Medical implants are often placed inside the body through invasive surgical procedures that can injure cells, tissues and organs. These injuries automatically trigger blood coagulation. The blood clot at the site of the injury stops the bleeding and provides temporary protection to the exposed wound site. The blood coagulation also serves as a short term platform for cells to attach, proliferate and migrate during the wound healing process. Furthermore, many chemical mediators are released during the wound healing process. Among the chemical mediators released are extra cellular matrixes (ECMs). The ECMs are proteins that stimulate cell adhesion, differentiation, proliferation and migration. These cell functions are very critical to the wound healing process and are mediated by cell adhesion molecules (CAMs), such as integrins, cadherins, selectins, etc., within the extracellular matrix (ECM). Cell ligand receptors within cell adhesion molecules regulate and interact with approaching cells. In many cases, these cell ligands are comprised of short peptide sequences, such as Arg-Gly-Asp (RGD) (SEQ ID NO: 2), found in many extracellular matrix proteins, including fibronectin, Arg-Glu-Asp-Val (REDV) (SEQ ID NO: 3), found in the type III

connecting segment region of fibronectin, Tyr-Ile-Gly-Ser-Arg (YIGSR) (SEQ ID NO: 5), and found in laminin, GIAG (SEQ ID NO: 9) or GTPGPQGIAGQRGVV (also known as P-15) (SEQ ID NO: 1), found in collagen. It has been found that cell adhesion molecules (CAMs) exhibit molecular features that are specific for recognition by circulating cells in vivo. These molecular features enhance cell adhesion, migration, proliferation, differentiation and the like which accelerate the short term and long term healing of wounds. These short peptides and their coatings on the surface of medical implants are useful for wound healing of vascular tissue, soft tissue, joints, bone and the like.

Since most biomaterials interact with surrounding cells at the interface, a great deal of attention has been paid to the development of surface properties that promote desirable interactions between biomaterials and surrounding cells. The development of biomimetic materials greatly depends on an understanding of how cells organize and direct specific interactions at the interface, so that new biomimetic materials can recognize, support, promote and interact with living cells of the surrounding tissues.

Information about the identity of short peptide sequences derived from native extracellular matrix proteins and their ability to promote cell adhesion and proliferation through the targeting of specific cell membrane receptors has led to the development of biomaterials with surfaces that express these biologically active sequences. (M.J. Humphries, 1993). The biomimetic systems of the current art are usually described in terms of ligands useful for enhanced cell adhesion, proliferation and migration, the related ligand structures, cell-binding activity and selectivity, functional linking groups connecting the ligands to the surface of the substrate by covalent bonding and the covalent bonding processes.

General Aspects

Biomemetic materials make it possible to regulate and control cellular interactions with implanted biomaterials at the molecular level. The receptor binding to the ligand that is externally presented from the biomemetic material determines the strength of the cell attachment to the implanted surface, the cell migration rate on or through the biomaterial and the extent of cytoskeletal organization. The biological responses depend on several factors, including but not limited to: receptor-ligand affinity, density of the ligand and spatial distribution and steric considerations of the ligand. Important design factors include, the spatial distribution, density and/or concentration of the active external peptides and the spacer (i.e. the linking structure between the substrate and the active ligands (e.g. peptides) which freely extend outward from the network (Shin, et al., 2003)).

Biomaterials play a very important role in most tissue engineering applications. Biomaterials can serve as a substrate to which cell populations migrate and attach, be implanted with a variety of specific cell or structure types, as a cell delivery vehicle and being utilized as a drug carrier to activate specific cellular functions (e.g. anti-inflammation, anti-thrombogenesis) in the local matrix (Shin, et al., 2003).

The useful biological activity of the specific active (typically short) peptide sequences (ligands) upon coupling to the substrate are retained. The modified peptide is flexible, experiences minimal steric hindrance and the terminal ligands are maximally configured to interact with the in vivo cellular environment. Bio-inert linear chains such as polyethylene glycol (of specific molecular weights) and some non-specific linear peptides are reported to have been placed between the solid phase surfaces and the active peptides (ligands) (Shin, et al., 2003).

Ligands (R) and Cell Binding, Proliferation and Migration

The role in cell binding of a β-bend is described within the triple helical region in collagen α1(I) chain by R.S. Bhatnagar, et al., 1997. The conformational preferences and biological activity of a synthetic 15-residue peptide, GTPGPQGIAGQRGVV (P-15) (SEQ ID NO: 1), are evaluated. A molecular mechanism is suggested for cell binding to collagen fibers based on a conformational transition in collagen molecules on the fiber surface.

The design of biomimetic habitats for tissue engineering with GTPGPQGIAGQRGVV (P-15) (SEQ ID NO: 1), a synthetic peptide analogue of collagen is described by R.S. Bhatnagar, et al., (1999) . The construction of biomimetic environments is described with a synthetic peptide analogue of collagen. A synthetic peptide ligand P-15 (SEQ ID NO: 1) for collagen receptors is utilized to show 3-D colony formation, increased osteogenic differentiation and deposition of highly oriented and organized matrix by human dermal and gingival fibroblasts and by osteoblast like HOS cells. (R.S. Bhatnagar, et al., Vol. 530).

Synthetic compounds and compositions having enhanced cell binding are described. The focus of these U.S. patents is the use of peptide structures similar to GTPGPQGIAGQRGVV (P-15) (SEQ ID NO: 1). Organic biomaterials covalently bonded to a substrate include the amino acid residue -Ile-Ala - folded in a β-bend are useful for enhanced cell binding. P-15 (SEQ ID NO: 1) and smaller fragments thereof are described. (R.S. Bhatnagar US Patents '736, '482, '428 and '348).

Ligand recognition by the I domain-containing integrins is described. Various integrins are used having active common amino acid domains, e.g. the metal ion-dependent adhesion site (MIDAS) motif. Human α_2 integrin and I domain bind the collagens laminin and echovirus 1. (S.K. Dickeson, et al., 1998).

Enhanced cell attachment is described for anorganic bone mineral in the presence of a synthetic peptide related to collagen. Human dermal fibroblasts are attached to anorganic bone mineral (ABM) particles. (J.J. Qian, et al., 1996). The attachment of cells is increased with increasing levels of GTPGPQGIAGQRGVV

(P-15) polypeptide (SEQ ID NO: 1) on the surface of the ABM particles.

A coating with genetic engineered hydrophobin is described which promotes growth of fibroblasts on a hydrophobic solid when the RGD (SEQ ID NO: 2) sequence is present. PTFE was found to have improved growth of fibroblasts by coating the solid with genetically engineered SC3 hydrophobin. (M.I. Janssen, et al., 2002).

The cellular recognition of synthetic peptide amphiphiles in self-assembled monolayer films is described. Looped RGD (SEQ ID NO: 2) amphiphiles promote adhesion, spreading and cytoskeletal reorganization of melanoma and endothelial cells. (T. Pakalns, et al., 1999).

The immobilization of RGD (SEQ ID NO: 2) to <111> silicon surfaces for enhanced cell adhesion and proliferation is described. Surface chemistry and microstructure need to be controlled to regulate cell behavior on biomaterial surfaces. RGD (SEQ ID NO: 2) surfaces are examined for fibroblast adhesion and proliferation. (D.H. Davis, et al. 2002).

Identification and validation of a novel cell-recognition site (KNEED) (SEQ ID NO: 11) on the 8th type III domain of fibronectin are described. Peptides containing the KNEED (SEQ ID NO: 11) sequence (of fibronectin) participate in cell attachment and spreading. (J.Y. Wong, et al., 2002).

The subject matter of some of these references overlaps with the following two topics:

Covalent Linking Groups

Co-regulation of cell adhesion by nanoscale RGD (SEQ ID NO: 2) organization and mechanical stimulus is described where the backbone of polymethyl methylate has a comb-like structure. Improved cell adhesion proliferation and density are observed. (LV. Koo, et al., 2002).

Organic linkers and spacers are described in the surface treatment of articles using a low temperature plasma treatment. These treated articles are used as grafts or stents and have biocompatible coatings. (M.H. Dang, et al., U.S.

6,159,531 and M.H. Dang, et al. (2003)).

Covalent Bonding to Substrate and Surface Modification

Coatings having biological activity and medical implants having a surface coating thereof and a method of manufacture using a low temperature plasma treatment is described. (M.H. Dang, et al., U.S. 6,159,531).

A multi-step method of forming a coating on a substrate such as a stent or a graft is described. The surface is treated with a plasma at or near atmospheric pressure. A bioactive/biocompatible coating and/or drug releasable coating is prepared. (Dang, et al., 2003).

Adhesion and proliferation of human endothelial cells on photochemically modified polytetrafluoroethylene (PTFE) is described. PTFE is surface modified by formation of C=O, C-OH, C-OOH and CNH_2 which improves cell adhesion and proliferation. (T. Gumpenberger, et al. Biomaterials in press - Internet publication, 2003).

Polymers are exposed to UV light in the presence of ammonia to study biomaterials-microvasculature interactions. Specific substrates include polytetrafluoroethylene and polyvinyl alcohol (PVA). This is a review which surveys work on reported biomaterial-microvasculature interactions with a focus on the use of biomaterials (containing, e.g. RGD (SEQ ID NO: 2), YIGSR (SEQ ID NO: 5), PDSGR (SEQ ID NO: 12), REDV (SEQ ID NO: 3), etc.) to regulate the structure and function of the microvasculature. (A.L. Sieminski, et al., 2000).

The synthesis and properties of amphiphilic networks 2: a differential scanning calorimetric study of poly(dodecyl methacrylate-*stat*-2,3 propandiol-1-methacrylate-*stat*-ethandiol dimethacrylate) networks and adhesion and spreading of dermal fibroblasts on these materials is described. Amphiphilic networks are utilized to produce hydrogels. Human skin fibroblasts are cultured on the hydrogels and observed to grow and spread. (R. Haigh, et al., 2002).

A composite expandable device for delivering into a vessel carrying blood is described. A coating is on the inner surface of the polymer sleeve which enhances cell growth on the sleeve. (L.V. Rudakov, et al., 2002).

Since cells interact with cell-binding peptides through cell adhesion domains that bind to localized regions within the molecules, the ability of cells to bind to the surface coated with the cell-binding peptide will be greatly affected by the orientation and conformation of the peptide on the surface relative to its cell adhesion domains. In addition, the number of cell adhesion domains within the peptide also influences cell behaviors on the surface, such as adhesion, spreading, growth, and migration (L.Y. Koo et al (2002).

All articles, references, U.S. patents, U.S. patent publications, U.S. patent applications, standards and the like are incorporated herein by reference in their entirety for background.

None of the references individually or jointly in combination with each other in any fashion teach or suggest the present invention.

From the above description, it is apparent that a need exists for an improved surface coating on implants to accelerate the in vivo healing process.

The present invention provides compositions of matter, pharmaceutical compositions, implants, methods of manufacture and methods of therapy to improve the cell adhesion, migration, proliferation and spreading involved with the healing process. Multiple arm peptides (MAP) of the present invention are a relatively large compared to most cell-binding peptides such as RGD (SEQ ID NO: 2), REDV (SEQ ID NO: 3) and YIGSR (SEQ ID NO: 5). Because of their large size, MAP peptides effectively provide the suitable molecular orientation and conformation for approaching cells. Their multiple cell adhesion domains on the multiple arms also greatly enhances the cell binding activity and selectivity. It is easier to synthesize mid-sized, branched peptides and attach them covalently onto different implant materials than large extra cellular matrix (ECM) proteins, such as fibronectin and collagen.

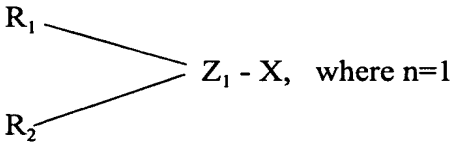
SUMMARY OF THE INVENTION

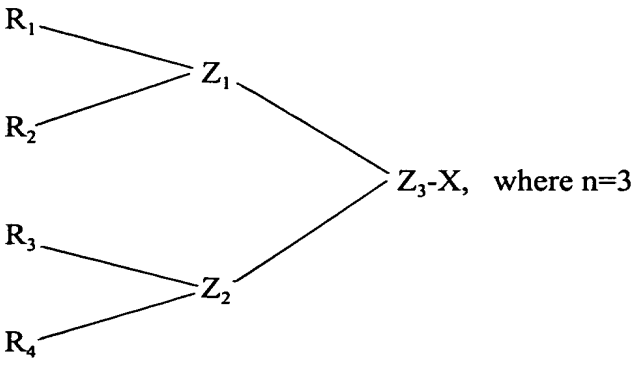
Composites of multiple arm peptides (or multiple antigenic peptides) and a substrate (MAP-S) of the present invention are useful for enhanced attachment, adhesion, migration, growing, organizing and differentiation of in vivo cells. They include a covalent organic structure (compound) having ligands that promote cell adhesion, attachment, migration, proliferation, differentiation and the like. The substrate S optionally being a matrix or having a modified surface is inert, solid, hydrogel or liquid, flexible, rigid, porous and/or non-porous.

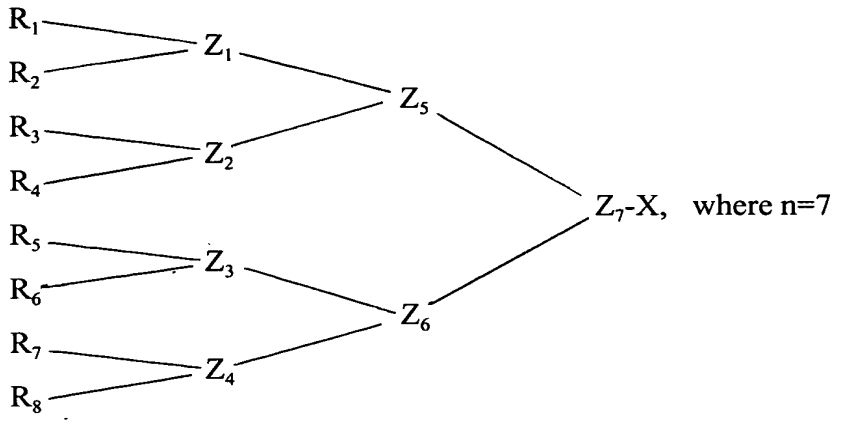
The present invention describes compositions of matter, pharmaceutical compositions and implants for the active structure MAP-S wherein MAP is a covalently bound organic structure which is covalently bound to a substrate S, wherein S selected from the group consisting of metal, alloy, ceramic, natural polymer, synthetic polymer, bioabsorbable polymer, and combinations and blends thereof, and the organic structure MAP is selected from:

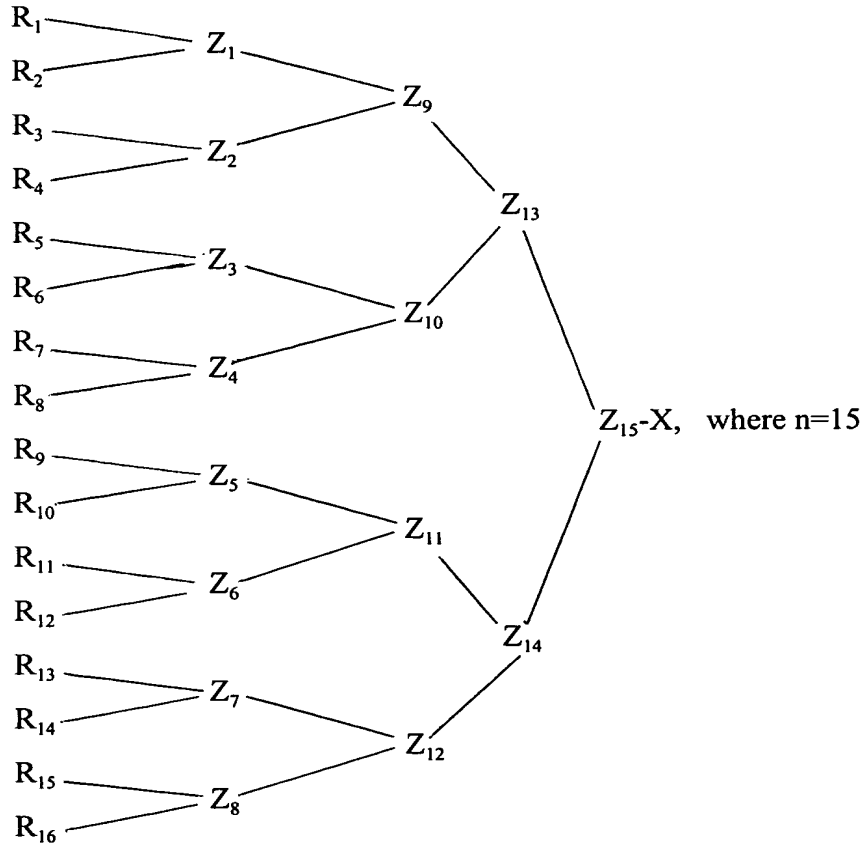
$(R)_{n+1} - (Z)_n - X$

where n is selected from 1, 3, 7 and 15, which produces the following exemplary structures:






R1
R2
R3
R4
R5
R6
R7
R8
Z1
Z2
Z3
Z4
Z5
Z6
Z7-X, where n=7


R1
R2
R3
R4
R5
R6
R7
R8
R9
R10
R11
R12
R13
R14
R15
R16
Z1
Z2
Z3
Z4
Z5
Z6
Z7
Z8
Z9
Z10
Z11
Z12
Z13
Z14
Z15-X, where n=15

R and Z in each MAP structure are the same or a different moiety. Each R (i.e. R_1 to R_{16} when present) may be any size or length and contains any type and number of cell-binding ligands and any type and number of other amino acids or anti-inflammatory or anti-thrombogenic structures. In addition, the MAP has at least one and optionally more than one active functional organic group to covalently link it to the surface of the substrate (S), where these active functional organic groups are a part of a group present: (i.e. a covalent part of X, Z or R).

X is an active or protected linking group selected from, but is not limited to, the group consisting of amine, one to five amino acids (X_1, X_2, X_3, X_4, X_5) which amino acids are the same or different, carboxylic acid, anhydride, hydroxyl, carbonyl, diol, disulfide (SH), hydroxyl succinimide (NHS) and siloxane;

Z (i.e., Z_1 to Z_{15} when present) is independently selected from, but is not limited to, the group consisting of lysine, polylysine, ornithine or any known tri-functional organic or inorganic linkers; and

R (i.e., R_1 to R_{16} when present) is independently selected from the group, but is not limited to,

GTPGPQGIAGQRGVV or P-15 (SEQ ID NO: 1);
RGD or Arg-Gly-Asp (SEQ ID NO: 2);
REDV or Arg-Glu-Asp-Val (SEQ ID NO: 3);
C/H-V or WQPPRARI or
Trp Gln Pro-Pro-Arg-Ala-Arg-Ile (SEQ ID NO: 4)
YIGSR or Tyr-Ile-Gly-Ser-Arg (SEQ ID NO: 5);
SIKVAV or Ser-Ile-Lys-Val-Ala-Val (SEQ ID NO: 6);
F-9 or RYVVLPRPVCFEKGMNYTVR or
Arg-Tyr-Val-Leu-Pro-Arg-Pro-Val-Cys-Phe -
Glu-Lys-Gly-Met-An-Tyr-The-Val-Arg (SEQ ID NO: 7);
HEP-III or GEFYFDLRLKGDK or
Gly-Glu-Phe-Tyr-Phe-Asp-Leu-Arg-Leu-Lys-Gly-Asp-
Lys (SEQ ID NO: 8);
GAG or Gly-Ile-Ala-Gly (SEQ ID NO: 9);

QGIAGQ or Gln-Gly-Ile-Ala-Gly-Gln (SEQ ID NO: 10);
KNEED or Lys-An-Glu-Glu-Asp (SEQ ID NO: 11);
PDSGR or Pro-Asp-Ser-Gly-Arg (SEQ ID NO: 12);
anti-inflammatory agents;
antithrombogenic agents; and
growth factor agents.

In one embodiment of the composition of matter, the substrate S is selected from a group consisting of hydroxylapatite, stainless steel, cobalt-chromium alloy, molybdenum alloy, titanium, titanium alloy, or a surface modified or unmodified polypropylene, polyethylene, polystyrene, polyether, polyamide/polyethylene copolymer, polychloroprene, polyester, polyvinyl chloride, polyolefin, polyphenolic, polyhydroxyacid, ABS epoxy, polytetrafluoro-ethylene, expanded polytetrafluoroethylene, polytetrafluoroethylene/polyethylene copolymer, fluorinated ethylene propylene, polyvinylidene, hexafluoropropylene, polyurethane, polysiloxane, polyisoprene, silicone, styrene butadiene, natural rubber, latex rubber, polyethyleneterephthalate, polycarbonate, polyamide, polyaramid, poly ether ketone, polyacetal, polyphenylene oxide, polysulfone, polyethersulfone, regenerated cellulose, polyamino acids, polyarylsulfone, polyphenylene sulfide, polybutylterephthalate (PBT) and combinations and blends thereof.

In one embodiment, in the composition of matter X is each independently selected from the group consisting of one to five amino acids (X_1, X_2, X_3, X_4 or X_5) and carboxylic acid.

In one embodiment, in the composition of matter Z_1 to Z_{15} in each MAP structure when present is lysine.

In one embodiment, in the composition of matter Z_1 to Z_{15} in each MAP structure when present is polylysine.

In one embodiment, in the composition of matter X_1 or X_2 are each independently selected from the group consisting of amino, amino acid, hydroxyl, and carboxylic acid.

Preferred MAP structures are those where n=1 (MAP2), n=3 (MAP4), n=7 (MAP8) and n=15 (MAP16). R (i.e. R_1 to R_{16} when the specific R group is present) is selected from the group consisting of GTPGPQGIAGQRGVV (SEQ ID NO: 1) , RGD (SEQ ID NO: 2), REDV (SEQ ID NO: 3), YIGSR (SEQ ID NO: 5), anti-inflammatory agents, anti-thrombogenic agents and combinations thereof.

Another important embodiment and advantage of the present invention is the use of amino acids, such as lysine, polylysine or ornithine as linkers to build the MAP structure. These structures are natural amino acids and are not expected to cause any detrimental in vivo effect (allergy, etc.) as may be likely with structures such as a polyethylene glycol, a conventional non-biological linking structure.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphic representation of human umbilical vein endothelial cells (HUVEC) growth of cells/cm^2 versus time in days.

Figure 2 is a graphic representation of a second example of human umbilical vein endothelial cells (HUVEC) growth of cells/cm^2 versus time in days.

Figure 3 is a graphic representation of human smooth muscle cells (HSMC) growth of cells/cm^2 versus time in days.

Figure 4 is a schematic representation of the multiple arm peptide MAP2 where the R, X , Z and S groups are defined in the Summary of the Invention above.

Figure 5 is a schematic representation of the multiple arm peptide MAP4 where the R, X , Z and S groups are defined in the Summary of the Invention above.

Figure 6 is a schematic representation of the multiple arm peptide MAP8 where the R, X , Z and S groups are defined in the Summary of the Invention above.

Figure 7 is a set of schematic MAP structures having specific amino acid lysine and alanine branching.

Figure 8 is a schematic representation of direct synthesis and indirect synthesis of MAP structures.

Figure 9 is a schematic representation of two different multiple arm peptides MAP8 connected to the surface of the substrate where the R, X , Z and S groups are defined in the Summary of the Invention.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Novel branched multiple arm peptides (or multiple antigenic peptides) (MAPs) and those MAPs which are covalently bonded to a substrate (S) are described as compositions of matter and as components of implants in the present invention. The covalently bound MAPs have at least one terminus (and optionally more than one terminus) attached to a substrate (S) and multiple arms which terminate in the same or different organic groups which have a variety of biological functions in vivo. These functions include but are not limited to increased cell adhesion, attachment, migration, proliferation, differentiation and the like, anti-inflammation properties, anti-thrombogenic properties, growth factor properties and the like.

The enhanced biological activity of the MAP-S structure of the present invention is believed to be achieved by providing an array of freely rotating active peptide sequences which can alter their confirmation and orientation to expose active domains for cell attachment, adhesion and other biological effects. These compounds also have an increased density of active domains which are covalently bonded and do not migrate in vivo.

Referring now to Figures 4, 5, 6 and 7, Figure 4 is a MAP2, Figure 5 is a MAP4 and Figure 6 is a MAP8. R, X, Z and S are described above in the Summary of the Invention. Figure 7 shows all three MAPs as specific for lysine and alanine. As can be seen in each of these figures, the multiple arms extend out from the surface into open space are therefore exposed for the close approach and attachment of cells (C), and antibodies (AB) and other useful biological factors in vivo.

The present invention also includes composites, implants and methods of use for promoting cell adhesion and other biological functions that comprise covalently attaching any of the above compositions of matter to a substrate (S, i.e. a matrix) and seeding living cells on the surface of the modified substrate. The substrates are listed above and in the Definitions which follow. Preferred substrates include biological or medical grade solids or biomaterials, i.e. those which are biologically compatible for in vivo applications and in vitro cell cultures. The invention is described in more detail below after the definitions of terms.

Definitions as used herein in alphabetical order include:

"Adhesive barrier" refers to those structures, which reduce the formation of connective tissue. See for example SEPRAFILM® adhesion barrier (a trademark of the Genzyme Corporation, Cambridge, Massachusetts). It is related to the polysaccharide hyaluronic acid found in connective tissue. (See also U.S. Patent 4,851,521.)

"Anti-inflammatory agents" refers generally to smaller organic structures which are known to reduce a present inflammation in in vivo tissues. Structures include but are not limited to aspirin, ibuprofen, naproxen, aminoacetophen, COX-2 inhibitors (e.g. VIOX) and the like.

"Bioabsorbable polymer" refers to polymers of the art that can be used as the substrates S such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), PGA + PLA copolymers, poly(orthoesters), poly(p-dioxanone) (PDS), poly β-hydroxybutyrate (PHB), poly(PHB-hydroxyvaleric acid), pseudo-poly(amino acids), poly(iminocarbonates) and the like. See Y.H. An et al., Biomaterials, Vol. 21, 2675-2652 (2000). It is sometimes used interchangeably with the term biodegradable polymer.

"Biodegradable polymer" refers to polymers of the art that can be used as the substrate S, and includes but is not limited to poly (L-lactide) (LPLA), poly glycolide (PGA), poly (DL-lactide) (DLPLA), poly (dioxanone) (PDO), poly (DL-lactide-co-L-lactide) (LDLPLA), poly (DL-lactide-co-glycolide) (DLPLG), poly (glycolide-co-trimethylenecarbonate) (PGA-TMC), poly (L-lactide-co-glycolide) (LPLG), poly (epsilon-caprolactone) (PCL) and the like. (See J.C. Middleton et al., Biomaterials, vol. 21, 2335-2346 (2000).

"Cell-binding Sequence CR" or "cell binding domain CD" refer to amino acid sequences in a polypeptide or protein which enhance binding of living cells.

"Combinations" refers in relation to polymer structures, any combination including, but not limited to, copolymers, multiple polymers, blends, laminates, emulsions and the like.

"F-9" refers to RYVVLPRPVCFEKGMNYTVR or Arg-Tyr-Val-Leu-Pro-Arg-Pro-Val-Cys-Phe-Glu-Lys-Gly-An-Tyr-The-Val-Arg (SEQ ID NO: 7) (A.S. Charonis, et al. Cell Biol. 107: 1253 (1998).

"Growth factor" refers to those structures which are known to have growth enhancing properties for cells in vivo, generally for specific cell and/or tissue types. The term includes but is not limited to hepatocyte-growth factor (HGF), epidermal growth factor (EGF), erythropoietin (EPO), fibroblast growth factor (FGF), insulin-like growth factor (IGF), interleukins, nerve growth factor (NGF), platelet derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF) and the like.

"HEP-Ilt or GEFYFDLRLKGDK" refers to Gly-Glu-Phe-Tyr-Phe-Asp-Leu-Arg-Leu-Lys-Gly-Asp-Lys (SEQ ID NO: 8) and a part of collagen (G.G. Koliakos, et al., J Biol. Chem 264: 2313-2332 (1989).

"Ligands" refers to the R groups of the structure herein (i.e. R_1 to R_{16} when

present in a MAP structure) which include structures which enhance cell adhesion, attachment, migration and proliferation, have anti-inflammatory properties, anti-thrombogenic properties, cell growth factor properties, adhesive barrier properties and the like. Different types of ligands R covalently bonded in the same MAP structure are contemplated.

"Optionally" refers to the invention when a component, bond, action, process step and the like may or may not be present. The invention is thus described whether or not that aspect is present or is not present.

"P-15" refers to GTPGPQGIAGQRCVV (SEQ ID NO: 1) and is found in collagen (R.S. Bhatnager, et al., Biomolec, Stucture & Dynam, 14(5): 547-560 (1997) and R.S. Bhatnager, et al., Tissue Engineering 5(1): 53-65 (1999)).

"R_1 to R_{16}" refers in the structures in the Summary to various groups (ligands) having properties as peptides, anti-inflammatory agents, anti-thrombogenic agents and the like activity in in vitro and in vivo systems.

"REDV" refers to Arg-Glu-Asp-Val (SEQ ID NO: 3), which is found in the type III connecting segment region of fibronectin (J.A. Hubbell, et al., Ann. N.Y. Acad. Sd. 665: 253-258 (1993).

"RGD" refers to a tri-amino acid sequence of the structure -Arg-Gly-Asp- (SEQ ID NO: 2) which is found in many adhesive plasma and extracellular matrix proteins, including fibronectin (see for example Hynes, Cell, 11-25 (1992); Hubbell, et al., Bio/Technology, 9, 568-572, (1991); Massia, et al., J. Biomed. Mater. Res., 25, 223-242, 1999; and Lin, et al., J. Biomed. Mater., Res, 28, 329-342, 1994).

"Substrate (S)" refers to but is not limited to solid, hydrogel or liquid materials. Substrate refers to, for example, the following: polymer materials selected from hydrocarbons including polypropylene, polyethylene, polystyrene,

polyether, polyamide/polyethylene copolymer, polychloroprene, polyester, polyvinyl chloride, polyolefin, polyphenolic, polyhydroxyacid, ABS epoxy, and corresponding copolymers and blends; fluorocarbons-including polytetrafluoroethylene, expanded polytetrafluorothylene, polytetrafluoroethylene/polyethylene copolymer, fluorinated ethylene propylene, polyvinylidene, hexafluoropropylene corresponding copolymers and blends; elastomers including polyurethane, polysiloxane, polyisoprene, silicone, styrene butadiene, natural rubber, latex rubber, and corresponding copolymers and blends; engineering thermoplastics including polyethyleneterephthalate, polycarbonate, polyamide, polyaramid, polyaryl ether ketone, polyacetal, polyphenylene oxide, polysulfone, polyethersulfone, regenerated cellulose, polyamino acids, polyarylsulfone, polyphenylene sulfide, polybutylphthalate (PBT), and the corresponding copolymers and blends thereof. Bioresorbable (or biodegradable) polymers such as poly(lactate) and poly(glycolide) are included (see above definitions). Hydrogel such as hydroxymethyl methacrylate (HEMA), hydroxymethyl acrylate, Di(hydroxymethyl) methacrylate, di(hydroxymethyl) acrylate, tri(hydroxyethyl) methacrylate, tri(hydroxymethyl) acrylate, and copolymers, blends and the like are included. Soluble polymers known in the art are also useful as substrate material. Mmetallic materials include stainless steel, cobalt-chromium-molybdenum alloy, pure titanium, and titanium alloys. In most applications the metallic and polymer materials have had their surfaces modified as is described herein to enhance the covalent bonding of the MAP structure.

"SIKVAV" refers to Ser-Ile-Lys-Val-Ala-Val (SEQ ID NO: 6) which is available from laminin (H.K. Kleinnman, et al. Vitamins and Hormones 47: 161-186 (1993).

"YIGSR" refers to Tyr-Ile-Gly-Ser-Arg (SEQ ID NO: 5), which is found

in laminin (S.P. Massia, et al., J. Biomed. Mater. Res., 25, 223-242, 1991).

"Z_{1-15}" refers in the structure in the Summary and Claim 2 to various organic structures which are used to create the covalent multiple armed structure having the active terminal groups R_1-R_{16}. Preferred Z_1 to Z_{15} groups (when present) include polyfunctional amino acids, such as lysine and polylysine.

The detailed description of the invention and preferred embodiments in R.S. Bhatnagar US Patent 5,354,736 is incorporated by reference here and it provides some useful description, preparations and background for the precursor peptides which are described in the present invention. Some precursor peptides as ligands are utilized in this invention in some MAP structures.

A suitable surface conformation is believed necessary for recognition by and the docking of living cells in vivo. The three-dimensional surface presented by the MAP region or parts of the MAP region are complementary to the reactive surface present on the cell-binding species (fibronectin). MAP compounds of the present invention mimic this surface ECM and any MAP compounds that can generate a similar surface are expected to have similar biological activity.

An embodiment of the present invention involves synthetic organic compositions of branched MAP structures that have enhanced biological activity functionally as compared to that of all or some portions of a single linear peptide chain. By "functionally comparable," is meant that the shape, size and flexibility of a MAP compound is such that the biological activity of the MAP compound is enhanced when compared to the biological activity of the single linear peptide chain or a portion thereof. Of particular interest to the present invention utilizing branched MAP structures is the property of significantly enhanced cell binding as compared to that observed for small linear peptides. Useful ligands are selected on the basis of similar spacial and electronic properties as compared to the linear

peptides or compounds. These individual ligands typically will be small molecules of amino acids of 100 or fewer or in the molecular weight range of up to about 10,000 daltons, and more typically up to 2,500 daltons. Inventive compounds are illustrated with synthetic MAP peptides; however, nonpeptide structures which mimic the necessary conformation for recognition and docking of cell-binding species are also contemplated as within the scope of this invention. For example, cyclic peptides or other compounds as R portions of the MAP structure in which the necessary conformation is stabilized by nonpeptides (e.g., thioesters) is one means of accomplishing the invention.

Of particular interest are the biological properties of the branched MAP compounds and composites which show increased cell binding in vitro of 50%, 100%, 250%, 500% or greater than is observed when compared to cell binding to a control surface. These in vitro results are a strong indicator that enhanced binding of the same magnitude or greater occurs and is useful in vivo. Each active terminal R group is preferably contemplated to be small covalently bonded molecules each of up to 50 amino acids or derivatives thereof. Examples of these small linear synthetic peptide groups as precursors for the ligands (R) of the MAP structures of the present invention include, but are not limited to, those found in Table 1 which includes sequence numbers.

Table 1. Linear Peptide Sequences as Precursors Provided for Reference

Description	SEQ ID NO:
GTPGPQGIAGQRGVV	1
RGD	2
REDV	3
C/H-V WQPPRARI	4
YIGSR	5
SIKVAV	6
RYVVLPRPVCFEKGMNYTVR	7
GEFYFDLRLKGDK	8
GIAG	9
QGIAGQ	10
KNEED	11
PDSGR	12
NH_2-GTPGPQGIAGQRGVV-lys-β-ala-COOH	13

Examples of inventive MAP peptides are found in Table 2 with MAP identification numbers.

Table 2

INVENTIVE PEPTIDES - MAP 2 STRUCTURES	MAP ID NO.:
$(NH_2$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_2$ - lys-β-ala-COOH	13
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_2$ - lys-lys-(NH_2)-β-ala-$CONH_2$	14
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_2$-lys-lys-(NH_2)-β-ala-COOH	15
$(NH_2$-Arg-Gly-Asp$)_2$-lys-β-ala-COOH	16
$(CH_3CO$ -Arg-Gly-Asp$)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	17
$(CH_3CO$ -Arg-Gly-Asp$)_2$ -lys-lys (NH_2)-β-ala-COOH	18
$(NH_2$-Arg-Glu-Asp-Val$)_2$-lys-β-ala-COOH	19
$(CH_3CO$-Arg-Glu-Asp-Val$)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	20
$(CH_3CO$-Arg-Glu-Asp-Val$)_2$-lys-lys-(NH_2)-β-ala-COOH	21

Table 2 (continued)

INVENTIVE PEPTIDES - MAP 4 STRUCTURES	MAP ID NO.:
$(NH_2$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_4$-$(lys)_2$-lys-β-ala-COOH	22
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_4$-$(lys)_2$-lys-(NH_2)-β-ala-$CONH_2$	23
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_4$-$(lys)_2$-lys-(NH_2)-β-ala-COOH	24
$(NH_2$-Arg-Gly-Asp$)_4$-$(lys)_2$-lys-β-ala-COOH	25
$(CH_3CO$-Arg-Gly-Asp$)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	26
$(CH_3CO$-Arg-Gly-Asp$)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	27
$(NH_2$-Arg-Glu-Asp-Val$)_4$-$(lys)_2$-lys-β-ala-COOH	28
$(CH_3CO$-Arg-Glu-Asp-Val$)_4$-(lys)-lys-lys-(NH_2)-β-ala-$CONH_2$	29
$(CH_3CO$-Arg-Glu-Asp-Val$)_4$-(lys)-lys-lys-(NH_2)-β-ala-COOH	30

TABLE 2 (continued)

INVENTIVE PEPTIDES - MAP 8 STRUCTURES	MAP ID NO.:
$(NH_2$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-β-ala-COOH	31
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	32
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	33
$(NH_2$–Arg-Gly-Asp$)_8$-$(lys)_4$-$(lys)_2$-lys-β-ala-COOH	34
$(CH_3CO$–Arg-Gly-Asp$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	35
$(CH_3CO$-Arg-Gly-Asp$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	36
$(NH_2$-Arg-Glu-Asp-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-β-ala-COOH	37
$(CH_3CO$-Arg-Glu-Asp-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	38
$(CH_3CO$-Arg-Glu-Asp-Val$)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	39

TABLE 2 (continued)

INVENTIVE PEPTIDES - MAP 16 STRUCTURES	MAP ID NO.:
$(NH_2$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys -β-ala-COOH	40
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	41
$(CH_3CO$-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	42
$(NH_2$–Arg-Gly-Asp$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-β-ala-COOH	43
$(CH_3CO$–Arg-Gly-Asp$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	44
$(CH_3CO$-Arg-Gly-Asp$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	45
$(NH_2$-Arg-Glu-Asp-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-β-ala-COOH	46
$(CH_3CO$-Arg-Glu-Asp-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-$CONH_2$	47
$(CH_3CO$-Arg-Glu-Asp-Val$)_{16}$-$(lys)_8$-$(lys)_4$-$(lys)_2$-lys-lys-(NH_2)-β-ala-COOH	48

In theoretical studies those MAP peptides having the inventive sequences: MAP ID NO: 13, MAP ID NO: 14 and MAP ID NO: 15, etc. show a high potential for conformations useful for cell adhesion, etc. The branches once synthesized are covalently defined and with the details provided in this application have generally predictable in vitro and in vivo properties.

Synthetic MAP peptides of this invention may or may not have a core sequence that has -Ile-Ala- formed in a β-bend at physiological conditions as described by R.S. Bhatnagar US Patent 5,635,482. In most embodiments, this specific bond is not present.

The synthetic MAP compounds of this invention also have one or more of the following properties: they promote cell migration into porous lattices; they bind to collagen receptors; they induce metalloproteinases; they can down-regulate prolyl hydroxylase and collagen; they inhibit inflammation: and they inhibit thrombogenesis. The enumerated properties (including promotion of cell attachment) of synthetic peptides for the inventive family is utilized to convey these highly desirable properties to composites for a wide variety of uses. The down-regulation of prolyl hydroxylase is of particular interest because it represents a key step in collagen synthesis. This means that MAP compounds of the invention can be used as inhibitors of collagen synthesis to block formation of scar tissue and thus promote scarless healing.

MAP peptides of the invention are preferably also substantially free of blocking groups (which are often used during peptide synthesis), such as t-butyloxycarbonyl group ("BOC").

Synthetic MAP peptides that have the desired biological activities may be produced at least of two general approaches.

Precursor polypeptides having fewer than about 100 amino acids, usually fewer than about 50 amino acids and more usually fewer than about 25, may be synthesized by the well-known Merrifield solid-phase chemical synthesis and modifications thereof method wherein amino acids are sequentially added to a growing chain, see B. Merrifield, *J. Am. Chem. Soc.*, 85:2149-56 (1963) and B. Merrifield, "Solid Phase Peptide Synthesis" in Peptides: Synthesis, Structure and Applications, B. Gutte, (ed), Academic Press, New York, p. 93-169 (1995). Linear peptides may be chemically synthesized by manual means or by automation in commercially available synthesis equipment.

Since the use of relatively short, linear peptides as ligands R (i.e., R_1 to R_{16} when present) is advantageous in performing the synthesis of MAPs described in the present invention, the peptides are preferably produced in quantity and will be free from contaminating substances, which are often found in peptides produced by recombinant techniques.

However, the linear synthetic peptides used as starting material for the MAP peptides of the present invention may also be synthesized by recombinant techniques involving the expression in cultured cells of recombinant DNA molecules encoding the gene for a desired portion for the α1(I) strand of collagen. The recombinant DNA procedures are well known in and available to one of skill in the art. DNA synthesis of specific peptide sequences is available from a variety of commercial services and is described in more detail in the R.S. Bhatnagar U.S. Patents '736, '428, 482, and '348.

The present invention also includes composites and methods of use (as implants) for promoting mammalian cell adhesion comprising attaching any of the above-described compositions of matter to a substrate (that is, a matrix) and adding cells to the composite. Substrates include, but are not limited to, those

listed in the Definitions section above. Some examples of composites MAP-S of this invention are shown below in Tables 3, 4, 5 and 6. It is understood that the functional group bond in X_1 to X_5 as described herein is the one that is covalently bonded (e.g. as a -COO- bond, a -CONH- bond, -NH – bond, etc.) to the surface of the substrate (S) as is described herein.

Table 3

Composites of the Invention Having Two (2) Arms

#	MAP ID	R	Z	X_1	X_2	S
8A	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	e-PTFE
8B	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	e-PTFE
8C	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-COOH	e-PTFE
8D	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	polyethylene
8E	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polyethylene
8F	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-COOH	polyethylene
8G	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	titanium alloy
8H	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	titanium alloy
8I	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-COOH	titanium alloy

Table 3 (continued)

Composites of the Invention Having Two (2) Arms

#	MAP ID	R	Z	X_1	X_2	S
8J	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	silicone
8K	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	silicone
8L	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-COOH	silicone
8M	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	polysulfone
8N	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
8O	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-COOH	polysulfone
8P	13	$R_1 = R_2 = NH_2$-P-15	Z_1 = lys	β - ala-COOH	-	polyurethane
8Q	14	$R_1 = R_2 = CH_3CO$-P-15	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
8R	15	$R_1 = R_2 = CH_3CO$-P-15	Z_1= lys	Lys (NH_2)	β-ala-COOH	polyurethane

Table 3 (continued)

Composites of the Invention Having Two (2) Arms

#	MAP ID	R	Z	X_1	X_2	S
8S	16	$R_1 = R_2 = NH_2$-RGD	Z_1 = lys	β-ala-COOH	-	ePTFE
8T	17	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	ePTFE
8U	18	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-COOH	ePTFE
8V	16	$R_1 = R_2 = NH_2$-RGD	Z_1 = lys	β-ala-COOH	-	polysulfone
8W	17	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
8X	18	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-COOH	polysulfone
8Y	16	$R_1 = R_2 = NH_2$-RGD	Z_1 = lys	β-ala-COOH	-	polyurethane
8Z	17	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
8AA	18	$R_1 = R_2 = CH_3CO$-RGD	Z_1= lys	Lys (NH_2)	β-ala-COOH	polyurethane
8AB	16	$R_1 = R_2 = NH_2$-RGD	Z_1 = lys	β-ala-COOH	-	HEMA
8AC	17	$R_1 = R_2 = CH_3CO$-RGD	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	HEMA
8AD	18	$R_1 = R_2 = CH_3CO$-RGD	Z_1= lys	Lys (NH_2)	β-ala-COOH	HEMA

Table 3 (continued)

Composites of the Invention Having Two (2) Arms

#	MAP ID	R	Z	X_1	X_2	S
8AE	19	$R_1 = R_2 = NH_2$-RGDV	Z_1 = lys	β-ala-COOH	-	ePTFE
8AF	20	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	ePTFE
8AG	21	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-COOH	ePTFE
8AH	19	$R_1 = R_2 = NH_2$-RGDV	Z_1 = lys	β-ala-COOH	-	polysulfone
8AI	20	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
8AJ	21	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-COOH	polysulfone
8AK	19	$R_1 = R_2 = NH_2$-RGDV	Z_1 = lys	β-ala-COOH	-	polyurethane
8AL	20	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
8AM	21	$R_1 = R_2 = CH_3CO$-RGDV	Z_1= lys	Lys (NH_2)	β-ala-COOH	polyurethane
8AN	19	$R_1 = R_2 = NH_2$-RGDV	Z_1 = lys	β-ala-COOH	-	poly(glycolide)
8AO	20	$R_1 = R_2 = CH_3CO$-RGDV	Z_1 = lys	Lys (NH_2)	β-ala-$CONH_2$	poly(glycolide)
8AP	21	$R_1 = R_2 = CH_3CO$-RGDV	Z_1= lys	Lys (NH_2)	β-ala-COOH	poly(glycolide)

Table 4

Composites of the Invention Having Four (4) Arms

#	MAP ID	R	Z	X_1	X_2	S
9A	22	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	–	e-PTFE
9B	23	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	e-PTFE
9C	24	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	e-PTFE
9D	22	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	–	polyurethane
9E	23	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
9F	24	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polyurethane
9G	22	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	silicone
9H	23	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	silicone
9I	24	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	silicone
9J	22	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	polysulfone
9K	23	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
9L	24	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polysulfone

Table 4 (Continued)

Composites of the Invention Having Four (4) Arms

#	MAP ID	R	Z	X_1	X_2	S
9M	25	$R_1 = R_2 = R_3 = R_4 = NH_2$-RGD	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	e-PTFE
9N	26	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	e-PTFE
9O	27	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	e-PTFE
9P	25	$R_1 = R_2 = R_3 = R_4 = NH_2$-RGD	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	polyurethane
9Q	26	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
9R	27	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polyurethane
9S	25	$R_1 = R_2 = R_3 = R_4 = NH_2$-RGD	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	silicone
9T	26	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	silicone
9U	27	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	silicone
9V	25	$R_1 = R_2 = R_3 = R_4 = NH_2$-RGD	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	polysulfone
9W	26	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
9X	27	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-RGD	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polysulfone

Table 4 (Continued)

Composites of the Invention Having Four (4) Arms

#	MAP ID	R	Z	X_1	X_2	S
9Y	28	$R_1 = R_2 = R_3 = R_4 = NH_2$-REDV	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	e-PTFE
9Z	29	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	e-PTFE
9AA	30	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	e-PTFE
9AB	28	$R_1 = R_2 = R_3 = R_4 = NH_2$-REDV	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	polyurethane
9AC	29	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polyurethane
9AD	30	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polyurethane
9AE	28	$R_1 = R_2 = R_3 = R_4 = NH_2$-REDV	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	silicone
9AF	29	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	silicone
9AG	30	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	silicone
9AH	28	$R_1 = R_2 = R_3 = R_4 = NH_2$-REDV	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	polysulfone
9AI	29	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	polysulfone
9AJ	30	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-REDV	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	polysulfone

Table 4 (Continued)

Composites of the Invention Having Four (4) Arms

#	MAP ID	R	Z	X_1	X_2	S
9AK	31	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	HEMA
9AL	32	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	HEMA
9AM	33	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	HEMA
9AN	31	$R_1 = R_2 = R_3 = R_4 = NH_2$-P-15	$Z_1 = Z_2 = Z_3$ = lys	β-ala-COOH	--	poly(glycolide)
9AO	32	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-$CONH_2$	poly(glycolide)
9AP	33	$R_1 = R_2 = R_3 = R_4 = CH_3CO$-P-15	$Z_1 = Z_2 = Z_3$ = lys	Lys (NH_2)	β-ala-COOH	poly(glycolide)

Table 5

Composites of the Invention Having Eight (8) Arms

#	MAP ID	R	Z	X_1	X_2	S
10A	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys -	β-ala -COOH	-	e-PTFE
10B	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	e-PTFE
10C	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	e-PTFE
10D	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polyurethane
10E	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polyurethane
10F	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polyurethane
10G	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys -	β-ala -COOH	-	silicone
10H	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	silicone
10I	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	silicone
10J	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polysulfone
10K	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polysulfone
10L	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polysulfone
10M	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys-	β-ala-COOH	-	Ti alloy
10N	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	Ti alloy
10O	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	Ti alloy

Table 5 (Continued)
Composites of the Invention Having Eight (8) Arms

#	MAP ID	R	Z	X_1	X_2	S
10P	34	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys -	β-ala -COOH	-	e-PTFE
10Q	35	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	e-PTFE
10R	36	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	e-PTFE
10S	34	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polyurethane
10T	35	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polyurethane
10U	36	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polyurethane
10V	34	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys -	β-ala -COOH	-	silicone
10W	35	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	silicone
10X	36	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	silicone
10Y	34	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polysulfone
10Z	35	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polysulfone
10AA	36	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polysulfone
10AB	34	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys-	β-ala-COOH	-	Ti alloy
10AC	35	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	Ti alloy
10AD	36	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	Ti alloy

Table 5 (Continued)
Composites of the Invention Having Eight (8) Arms

#	MAP ID	R	Z	X_1	X_2	S
10AE	37	R_1 to R_8 - all NH_2-REDV	Z_1 to Z_7 all = lys -	β-ala -COOH	-	e-PTFE
10AF	38	R_1 to R_8 - all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	e-PTFE
10AG	39	R_1 to R_8- all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	e-PTFE
10AH	37	R_1 to R_8 - all NH_2-REDV	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polyurethane
10AI	38	R_1 to R_8 - all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polyurethane
10AJ	39	R_1 to R_8- all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polyurethane
10AK	37	R_1 to R_8 - all NH_2-REDV	Z_1 to Z_7 all = lys -	β-ala -COOH	-	silicone
10AL	38	R_1 to R_8 - all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	silicone
10AM	39	R_1 to R_8- all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	silicone
10AN	37	R_1 to R_8 - all NH_2-REDV	Z_1 to Z_7 all = lys-	β-ala-COOH	-	polysulfone
10AO	38	R_1 to R_8 - all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	polysulfone
10AP	39	R_1 to R_8- all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	polysulfone
10AQ	37	R_1 to R_8 - all NH_2-REDV	Z_1 to Z_7 all = lys-	β-ala-COOH	-	Ti alloy
10AR	38	R_1 to R_8 - all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	Ti alloy
10AS	39	R_1 to R_8- all CH_3CO-REDV	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	Ti alloy

Table 5 (Continued)

Composites of the Invention Having Eight (8) Arms

#	MAP ID	R	Z	X_1	X_2	S
10AT	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys -	β-ala -COOH	-	HEMA
10AU	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	HEMA
10AV	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	HEMA
10AW	31	R_1 to R_8 - all NH_2-P-15	Z_1 to Z_7 all = lys-	β-ala-COOH	-	poly(glycolide)
10AX	32	R_1 to R_8 - all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	poly(glycolide)
10AY	33	R_1 to R_8- all CH_3CO-P-15	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	poly(glycolide)
10AZ	31	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys -	β-ala -COOH	-	HEMA
10BA	32	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	HEMA
10BB	33	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	HEMA
10BC	31	R_1 to R_8 - all NH_2-RGD	Z_1 to Z_7 all = lys-	β-ala-COOH	-	poly(glycolide)
10BD	32	R_1 to R_8 - all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-$CONH_2$	poly(glycolide)
10BE	33	R_1 to R_8- all CH_3CO-RGD	Z_1 to Z_7 all = lys-	lys-NH_2	β-ala-COOH	poly(glycolide)

Table 6

Composites of the Invention Having Sixteen (16) Arms

#	MAP ID	R	Z	X_1	X_2	S
11A	40	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	e-PTFE
11B	41	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	e-PTFE
11C	42	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	e-PTFE
11D	40	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polyurethane
11E	41	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polyurethane
11F	42	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polyurethane
11G	40	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	silicone
11H	41	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	silicone
11I	42	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	silicone
11J	40	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polysulfone
11K	41	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polysulfone
11L	42	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polysulfone

Table 6 (Continued)

Composites of the Invention Having Sixteen (16) Arms

#	MAP ID	R	Z	X_1	X_2	S
11M	43	R_1 to R_{16} - all NH_2-RGD	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	e-PTFE
11N	44	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	e-PTFE
11O	45	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	e-PTFE
11P	43	R_1 to R_{16} - all NH_2-RGD	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polyurethane
11Q	44	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polyurethane
11R	45	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polyurethane
11S	43	R_1 to R_{16} - all NH_2-RGD	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	silicone
11T	44	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	silicone
11U	45	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	silicone
11V	43	R_1 to R_{16} - all NH_2-RGD	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polysulfone
11W	44	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polysulfone
11X	45	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polysulfone

Table 6 (Continued)

Composites of the Invention Having Sixteen (16) Arms

#	MAP ID	R	Z	X_1	X_2	S
11Y	46	R_1 to R_{16} - all NH_2-REDV	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	e-PTFE
11Z	47	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	e-PTFE
11AA	48	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	e-PTFE
11AB	46	R_1 to R_{16} - all NH_2-REDV	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polyurethane
11AC	47	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polyurethane
11AD	48	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polyurethane
11AE	46	R_1 to R_{16} - all NH_2-REDV	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	silicone
11AF	47	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	silicone
11AG	48	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	silicone
11AH	46	R_1 to R_{16} - all NH_2-REDV	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	polysulfone
11AI	47	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	polysulfone
11AJ	48	R_1 to R_{16} - all CH_3CO-REDV	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	polysulfone

Table 6 (Continued)

Composites of the Invention Having Sixteen (16) Arms

#	MAP ID	R	Z	X_1	X_2	S
11AK	46	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	HEMA
11AL	47	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	HEMA
11AM	48	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	HEMA
11AN	46	R_1 to R_{16} - all NH_2-P-15	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	poly(glycolide)
11AO	47	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	poly(glycolide)
11AP	48	R_1 to R_{16} - all CH_3CO-P-15	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	poly(glycolide)
11AQ	46	R_1 to R_{16} - all NH_2-RGD5	Z_1 to Z_{15} all = lys -	β-ala-COOH	-	HEMA
11AR	47	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - $CONH_2$	HEMA
11AS	48	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	HEMA
11AT	46	R_1 to R_{16} - all NH_2-RGD	Z_1 to Z_{15} all = lys-	β-ala-COOH	-	poly(glycolide)
11AU	47	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys- NH_2	β - ala - $CONH_2$	poly(glycolide)
11AV	48	R_1 to R_{16} - all CH_3CO-RGD	Z_1 to Z_{15} all = lys-	lys-NH_2	β - ala - COOH	poly(glycolide)

The mode of attachment to the substrate is via covalent linkages. Covalent linkages include, but are not limited to, those involving ester, amide, anime or ether, see Carey et al., *Advanced Organic Chemistry*, Part B, Plenum Press, New York (1983). An exemplary method of covalent linkages involves peptides of the present invention with additions of amino acids at either the N-terminus or C-terminus to provide for binding or conjugation of the peptide to a solid phase or another protein.

Preferred types of cells to be adhered to the MAP structures include endothelial cells; however, most, if not all, cell types may be used.

Because endothelial cells play the central role of lining the unique vascular system in the living organism in the processes of the wound healing, it makes the in vitro use of endothelial cells as a model an important focus of biomaterial research. Since the original technique of cultivating human endothelial cells in vitro published in 1973 by E.A. Jaffe et al (J. Clin. Invest., 52, 2745ff (1973)), our knowledge of the endothelium has been altered from it being a passive barrier between the blood and the vessel wall to being a highly dynamic tissue with fundamental regulatory roles in numerous physiological processes (C.J. Kirkpatrick, Int. J. Microcirc, 17, 231ff (1997)).

The endothelium regulates four principal areas of biological function:

1. Hemostatic control is achieved by the endothelium to maintain a delicate balance between pro- and anti-thrombogenic signals.

2. The endothelium is involved in growth control by producing growth factors, such as platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) in response to cytokine stimulation.

3. The endothelium exerts a vital controlling function in vascular tone, principally by the synthesis of nitric oxide and prostacyclin as potent

vasodilators.

4. The endothelium is a central regulator of the inflammatory response.

Because of these important regulatory functions of the endothelium, the promotion of endothelization on the surface of implants is vital for blood contacting devices. Therefore, the use of endothelial cells in the evaluation of new biomaterials and biosurfaces becomes very advantageous and imperative.

Biological Testing and Results

A more detailed description of the preparation and biological in vitro testing of Figures 1, 2 and 3 follows below.

In a specific embodiment, the present invention concerns peptide coated expanded polytetrafluoroethylene (ePTFE) stent graft materials in vitro using human umbilical vein endothelial cells (HUVEC). Four types of samples are studied: PTFE control (PTFE), chemical activated PTFE (P+C), GTPGPQGIAGQRGVV or (P-15) coated ePTFE (P-15), and MAP4 coated ePTFE (MAP4). Two identical experiments were carried out to obtain statistically reliable cell growth data. A similar plasma surface coating method described by M.H. Dang in U.S. Patent 6,159,531 and also in U.S. patent publication 20030113478 (2003) was used to covalently bond peptides onto ePTFE films. The coated ePTFE samples were studied in vitro by seeding HUVEC onto their surfaces through a well established cell culture method. Results showed that MAP4 coated ePTFE had the largest increase in cell adhesion and cell proliferation over the ePTFE control. The cell adhesion of MAP4 coated ePTFE after 24 hours was more than 2.5 times better than that on ePTFE control. There were 400 percent more living cells on MAP4 coated ePTFE than that on ePTFE control after 4 days of incubation. MAP4 coated ePTFE was also more cell-

promoting than P-15 coated ePTFE. It is believed that the superior cell-promoting properties exhibited by the MAP (e.g. MAP4) coating on ePTFE are due to its multiple cell adhesion domains within the MAP molecule and its large size to form suitable orientation and conformation for approaching cells. Similar cell growth data were found for both P-15 coated and chemical activated ePTFE samples.

Much of the discussion herein has focused in the use of small peptides as terminal ligands. Some specific features of the invention are described below with other uses and advantages then being apparent using the detailed information described herein to be apparent one of ordinary skill in the art.

Multiple-Arm Peptide (MAP) - (Linking groups)

The key feature of the MAP system is the many fold amplification of a peptide in a chemically defined manner. Unlike random polymerization which usually produces linear arrays of a wide range of polymers, the MAP polymer system produces branched covalently bonded polymers in a controlled manner having unambiguous structures. (In fact it was determined as part of these studies that a simple dimer of an active peptide, such as P-15-P-15, when tested showed little or no enhancement of cell adhesion, migration, differentiation or the like over the mono-peptide.) In the cascade type of MAP system, this structure is obtained by using a core matrix as a scaffolding consisting of several sequential ends of a tri-functional groups, such as an amino acid as a building unit. Lysine is the most commonly used because its two ends that amino acid groups are available for the branching. Other amino acids such as ornithine have also been used with success. When lysine is used, the core matric is unsymmetrical with a longer arm consisting of a side chain and a short arm consisting of the amino group. In the case of MAP 8 having three levels of branching, amino groups varying distance from 7 to 18 carbon atoms from the first branched carbon atom are observed. A symmetrical core is designed of lysine and alanine as a building unit. Further sequential propagation of lysine produces MAPs of tetravalent

(MAP 4) or octavalent (MAP 8) or hexadecavalent (MAP 16), etc., reactive ends which are biologically active. MAP synthesis is now commercially available under contract with a number of companies. Usually, the MAP synthesis starts with a core of lysine-alanine or -lysine-lysine (NH_2)-ala- and builds the desired MAP structures.

A MAP structure was first described by J.P. Tam, Proc. Natl. Acad., SCI USA 85, 5409-13 (1988) and summarized by J.P. Tam, "Synthesis and Applications of Branched Peptides and Immunological Methods and Vaccines" in Peptides: Synthesis, Structures and Applications, B Sutte, (ed), Academic Press, San Diego, CA, 455-500 (1995) and later reported by W. Huang et al., Mol. Immunol, 31, 1191-99 (1993), and MAP syntheses are also described by J.P. Tam in US Patent 5,580,563 and I. Toth et al. in US Patent 5,882,645, all of which are incorporated by reference in their entirety.

In one embodiment, the multiple arm peptides of the present invention are usually polypeptides (or protein) which have a high-density cluster of active terminal peptides which may account for over 90% of the total molecular weight of the MAP and which surround the smaller multi-branching lysine core. The backbone of this type of MAP is made up of amide bonds and typically these MAPs are remarkably stable in solution between pH 2 and 9. Thus, the MAPs can be prepared, stored and shipped as a lypholized powder.

With the lysine structure of this embodiment, a polarity preference is created when groups are attached to the core matrix for a C to N when it is synthesized in the conventional Merrifield type solid state synthesis. The conventional Boc-Benzyl-tert-butylcarbonyl chemistry or Fmoc-tert-butylfluorenyl-methoxycarbonyl chemistry is similar to that of a linear peptide with some modifications which within this application are with the skill in the art.

If a carboxyl group is being added, an indirect modular method is used. The two methods, direct and indirect, are shown in schematic form in Figure 8. The indirect approach overcomes a lack of flexibility in the orientation of a peptide. It consists of the synthesis of a functionalized core matrix and unprotected peptides separately followed by chemoselective ligation of the two

components. See for example J.P. Tam, 1995, p 460.

Ligands functioning as anti-inflammatory agents

In another embodiment of this invention, the MAP motif is used to bind anti-inflammatory agents at the end of one or more of the branches present. Anti-inflammatory agents such as 2-acetoxybenzoic acid (aspirin), 2-(4-isobutylphenyl) propionic acid (ibuprofen), d-2-(6-methoxy-2-naphythyl) propionic acid (naproxen) and, COX-2 inhibitors (i.e. VIOX) are known anti-inflammatory agents used in a wide variety of therapeutic products. Each has a free unprotected carboxyl group which can be utilized by one of skill in the art in the Merrifield (1963) solid state synthesis described above.

In one embodiment, these anti-inflammatory agents are covalently coupled via the carboxylic acid to the free amine of the lysine to create an active amide bond. Thus, the terminal lysine in each of the short branches of MAP2, MAP4, MAP8 or MAP16 is terminated with an anti-inflammatory group. Another embodiment is to increase the length of each amino acid branch of MAP with a number of standard amino acids (e.g., one to eight) then couple the anti-inflammatory agent to the final free amine group then in the terminal position by standard Merrifield solid state synthesis methods. Thus the R group in the MAP structure described herein has anti-inflammatory properties as the anti-inflammatory group is covalently coupled to 1 to 8 linking amino acids in each branch of the MAP.

Ligands Functioning as Anti-thrombogenic Agents

In another embodiment of this invention, the MAP motif is used to bind anti-thrombogenic agents at the ends of one or more of the branches which are present. Suitable anti-thrombogenic agents include heparin (both high and low molecular weight), coumarin, hirudin (a polypeptide having a molecular weight of about 10,800) and its analogs and the like.

These agents are coupled through these agents' active functional groups (e.g. $-NH_2$) in the manner described above for the anti-inflammatory agents.

Alternatively, an amino acid chain of 1-8 amino acids is synthesized terminating in an amino group. Thus, the heparin amino group and the terminal amino group are then covalently coupled, using for example, an organic diacid, such as succinic acid and are ligands in the MAP structure.

Ligands Functioning as Growth Factor Agents

In another embodiment of this invention, the MAP motif is used to covalently bind growth factor agents at the ends of one or more of the MAP branches which are present. Suitable growth factor agents include but are not limited to VEGF, PDGF and the other listed above in the Definitions.

These growth factors are coupled through these agents' active functional groups (e.g. $-NH_2$, -COOH, etc.) in the manner described above for the anti-inflammatory agents.

Alternatively, an amino acid chain of about 1-8 amino acids is synthesized terminating in an amino group. Thus, the growth factor amino group and the terminal amino group are then covalently coupled, using for example, an organic diacid, such as succinic acid and become ligands in the MAP structure.

Ligands Functioning as Adhesive Barrier Agents

In another embodiment of this invention, the MAP motif is used to covalently bind adhesive barrier agents at the ends of one or more of the branches which are present. Suitable adhesive barrier agents include SEPRAFILM, DACRON or any of the materials known in the art to be used to combat the adhesion of unwanted cells or tissue.

These agents are coupled through these agents' active functional groups (e.g. $-NH_2$, -COOH, etc.) in the manner described above for the anti-inflammatory agents.

Alternatively, an amino acid chain of 1-8 amino acids is synthesized terminating in an amino group. Thus, surface amino groups of the adhesive barrier and the terminal amino group are then covalently coupled, using for example, an organic diacid, such as succinic acid and are ligands in the MAP

structure.

Formation of MAP-S

The synthetic MAP peptides are synthesized as is described herein. The MAP-structure (MAP-S) structure is formed by a number of processes. A preferred process is the plasma treatment described by M.H. Dang in US Patent 6,159,531 and also in US patent publication 20030113478 (2003). MAP peptides with active covalent linking groups are reacted with plasma treated and chemically activated substrate (S) (i.e., ePTFE or the other substrates listed in the Definitions above) as described in US Patent 6,159,531, which has organic functional groups on its surface. The resulting MAP-S article washed vigorously with water, ethanol or combinations thereof to remove free (non-covalently bonded) MAP peptides. The MAP article is then tested to confirm that the MAP-S covalently bonding to the surface coating has been obtained. Surface test methods include Amino Acid Analysis, MS, XPS, ATR-IR and other surface analytical techniques known in this art.

One MAP Structure having Different Ligands (R)

Another embodiment of the invention is to provide a MAP-S structure which have different ligands (R) on the same MAP structure. This is achieved by creating the first (MAP 2), second (MAP 4) and third generation (MAP 8) of the "tree" structure. Mixtures (in a ratio of about 50/50 or 33/66) of terminal ligands as a cell adhesion peptide R_1 and a second ligand R_2, for example, an anti-inflammatory agent are added and covalently coupled to create the mixed ligands R_1-, R_2 – on the surface of the substrate. The amount of each of the different ligands which are covalently attached is determined by the reaction conditions, the ratios of the precursor R groups, type of R group, and attachment of both types of ligands R to the substrate S is observed.

Two MAPs Having Different Ligands Attached to Substrate Surface

Another embodiment of this invention is to provide a MAP-S structure

which has multiple biological properties. In this embodiment, two MAP compositions, one MAP (9A) having ligands selected from peptides useful for cell adhesion, and the other MAP (9B) having ligands useful as anti-inflammatory agents are covalently attached to a substrate (S) structure are prepared. (See Figure 9) These two different MAP structures are then combined in a ratio of 50/50 to 33/66 and subjected to the standard covalent coupling described herein to the surface of a modified substrate S. The biological properties in vivo of the MAP-S article thus produced have both enhanced cell adhesion properties and enhanced anti-inflammation properties as compared to a single strand cell adhesion peptide or a single anti-inflammatory group. This approach is easily extended to produce and test the corresponding MAP8 and MAP16 structures.

Similarly three different ligand groups R_1 , R_2 and R_3 cell migration groups are added to the surface of a treated substrate S by combining for example a 33/33/34 mixture of the R_1 , R_2 and R_3 and immediately covalently coupling to the precursor MAP4 , MAP8 and MAP16 structure as is described above.

MAP Crosslinking to Substrate S

Because of the many structures possible in the MAP2, MAP4, MAP8 and MAP16, it is also possible to synthesize structures which have multiple active covalent bonding sites 2, 3, 4, etc. for attaching to the substrate S. Thus, in the covalent MAP structures shown in the Summary above R and Z in addition to X may have an active (unprotected) functional group (such as an amine, amide, or carboxylic acid) which will, under the proper circumstances, also covalently bond to substrate (S). This creates an organic cross linked structure.

MAP-S as a Pharmaceutical Composition

In another embodiment, this invention also includes MAP-S neat or in combination with a pharmaceutically acceptable carrier are used as a pharmaceutical composition to improve wound healing. The MAP2, MAP4 or MAP8 is covalently bonded to substrate S, such as finely powdered hydroxylapatite, etc. This MAP-S is then contacted with a wound, bone break or

injury in need of accelerated repair. Enhanced healing with the use of MAP-S is observed.

Testing of a MAP-S Structure and its Properties

Example 9 below describes the test procedure and results to establish that MAP-S covalent bonding to the surface has occurred. Example 11 also describes the enhanced cell adhesion, migration, proliferation, etc., that is observed in vitro for the MAP structure as compared to uncoated substrate surface and the single strand of for example P-15. These in vitro results are indicative of the same enhanced cell adhesion, etc. that occurs in vivo with MAP-S composites of this invention. Example 12 describes the results of an experiment which shows that smooth muscle cell growth is not enhanced which is another benefit of the MAP structures of the present invention.

Primary Human Umbilical Vein Endothelial Cells (HUVEC) were selected to evaluate peptide coated ePTFE stent graft materials. HUVEC is the most widely used human endothelial cell type in biomaterial research. HUVEC is more sensitive to different surfaces, but less stable and slower in growth than transformed cells. These Experiments are described below.

Two identical experiments discussed below were conducted to make certain that cell growth data were statistically reliable.

The following Examples are to be read as being illustration and exemplary only. They are not to be construed as being limiting in any way or manner.

Materials

ePTFE graft films with a thickness of 0.002 inch were obtained from Pall Corporation, Port Washington, NY.

Cell Culture – HUVEC cells were purchased from Clonetics, Cumbrous Corp., East Rutherford, NJ, Lot 3F0150. Cells were initiated from P2 frozen stock to P3 and P3 cells were seeded on sample films at a density of 10,000 cells/cm^2. The cell culture assays in the protocol were followed of "In Vitro Study of P-15 and MAP4 Coated ePTFE Stent Graft Materials."

Peptide Coating

Peptide coating procedures were followed in the protocol of "In Vitro Study of P-15 and MAP Coated ePTFE Stent Graft Materials." Both sides of ePTFE films were plasma treated.

Methods

Synthesis of MAP Peptides

MAP peptides having fewer than about 100 amino acids (and often less than about 50 amino acids) are synthesized by the conventional Merrifield solid phase peptide synthesis (SPPS) and modifications thereof. The amino acids are sequentially added to a growing chain (see, for example, B. Merrifield, J. Am. Chem. Soc., 85, 2149-56 (1963), (B. Merrifield, 1995) and J. Nestor, et al. U.S. Patent 4,318,905). The basic principle for solid phase peptide synthesis (SPPS) involves the stepwise addition of amino acids to the growing oligopeptide chain that is anchored to a chemically stable solid particle. Thus the particle can be separated from solvents and reagents during its synthesis by simple filtration. Once the synthesis is complete the chain is cleaved from the support and purification takes place in solution.

Automatic peptide synthesis equipment is available from commercial supplies such as Advanced Chemtech, Louisville, KY, Applied Biosystems, Foster City, CA and Beckman Instruments, Inc., Wladwich, NJ.

For example, a MAP4 peptide, $(HN_2$-Gly-Thr-Pro-Gy-Pro-Gln-Gly-Ile-Ala-Gly-Gil-Arg-Gly-Val-Val-$CONH_2)_4$-$(Lys)_2$-Lys-β-Ala-OH was synthesized by a sequence of standard organic chemical reactions using the Merrifield solid phase peptide synthesis (Merrifield, 1995 & Tam, 1995) as is described above and below.

Table 7 below summarizes the details of the synthesis of MAP4 and is adapted for the preparation of MAP structures.

Table 7*

	MAP4
Instrument	Model 90 (Advanced ChemTech)
Resin	Fmoc-β-ala-Wang Resin
Deprotection	25% Peperidine/DMF 1 x 5 min, 1 x 20 min
Coupling	DIC
Activation	HOBt
Monitoring	Kaiser Ninhydrin test
Solvent	DMF/DCM/NMP for coupling DMF/MeOH/DCM for washing
Cleavage	TFA: water: triisopropylsilane 95:2.5:2.5:3 Hours

*Researchers need to follow or adapt the equipment manufacturer's instructions to produce these and the other polypeptides for use in the present invention.

Covalent Bonding of Peptides of Substrates (S)

Peptides are covalently bonded to the surface of substrates (S) through a similar plasma method described by M.H. Dang in US Patent 6,159,531 and also in US patent application 20030113478 (2003). In summary, substrates (films, rods or tubes) are treated with atmospheric or low pressure plasma for a period of time at a given intensity. The plasma treated samples are then chemically activated using a mixture solution, such as sodium hydroxide and chloroacetic acid. Peptides, linear or MAP, are covalently bonded to the chemically activated substrates using the well-known coupling agents, such as ethyldiethylaminopropylcarbodiimide (EDC), with or without the addition of N-hydroxysuccinimide (NHS), glutaraldehyde, dimethylpimelidate, dissucinimidyl

suberate (DSS) and succinimidyl 4-(N-maleimidomethyl)cycloexane-1-carboxylate (SMCC). The covalent bonding process usually occurs at ambient temperature and slightly acidic conditions.

Cell Culture

Well-established culture practices are used (see, for example, R. Ian Freshney, Culture of Animal Cells, Wiley-Liss, 2000) to assess the effectiveness of inventive peptides on different substrates. Peptide bonded substrates are die-cut into disks and then attached to the bottom of cell culture plates using medical grade transfer tapes such as 9877 from 3M Corp., St. Paul, MN. Disk samples are sterilized by ETO or with 70% sterile ethanol for at least two hrs. Primary human cells, such as HUVEC and HSMC, along with the recommended cell culture media are used. Cells are counted at different time point using the Hemocytometer cell counter system from Fisher Scientific, Hampton, NH.

EXAMPLE 1

PREPARATION OF A MAP4

$(NH_2\text{-GTPGPQGIAGQRGVV})_4\text{-}(Lys)_2\text{-Lys-}\beta$ ala-COOH

(a) The MAP4 peptide, (NH_2-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val)$_4$-$(Lys)_2$-Lys–β-Ala-COOH was assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling was accomplished with the specific amino acid sequence of the MAP4 peptide. Coupling of all other Fmoc amino acids for the desired sequence was accomplished using 3 equivalents of 1-Hydroxybenzotriazole (HOBt) and 3 equivalents of 1,3 diisopropylcarbodiimide (DIC). Coupling times of about 120 min were employed. After each coupling the protected peptide Wang resin intermediate was washed as before with 3 volumes each of DMF, methanol and DCM. The completeness after the coupling and cleavage reactions were monitored by the Kaiser Ninydrin test. Following the addition of the last Fmoc-residue and following the deprotection of the Fmoc-group, the peptide Wang resin intermediates was again washed with DMF, methanol and DCM, then air dried.

Peptides were cleaved from the resin using a mixture consisting of trifluoroacetic acid: water: triisopropylsilane. (95:2.5:2.5) and stirred for 60 min at ambient temperature. The respective peptides were isolated by precipitation with diethyl ether and dried at room temperature.

Purification and Analysis of Inventive Peptides - - Inventive peptides were purified using preparative reverse-phase liquid chromatography (RP-HPLC)on a C-18 support (Detapak 4.0cm x 30cm, 15μ, 300Å with a gradient of 0-50% B over 50 min. Buffer A consisted of TFA (0.1%) in water and 'Buffer B consisted of acetronitrile (with 0.1% TFA). A flow rate of 150 mL/min was employed. Fractions of 1 min (150mL) were collected. The purity of these fractions was checked by analytical RP-HPLC and fractions containing >95% pure target peptide were cooled and lyophilized overnight. The resulting dried respective peptides were assayed again by analytical RP-HPLC to yield preparations with peptides of >95% target peptides. Finally the purified peptides were analyzed by mass spectrometry (MS) to verify the purity and targeted molecular formula. In some case, peptides are also analyzed by Amino Acid Analysis to verify the ratios of amino acids in the molecule. Typical analytical results are listed in the following Table 8.

Table 8. Typical Analytic Results for Inventive Peptides

Peptide	MAP 4 Peptide: (NH_2-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)$_4$-(Lys)$_2$-Lys-β-Ala-COOH
Calculated Molecular Formula	$C_{257}H_{435}H_{87}H_{77}$
Theoretical Molecular Weight (g/mole)	5975.87
Found Molecular Weight by Mass Spectroscopy (g/mole)	5975±2
Purity by Analytical RP HPLC	>95%

(a1) Alternatively, the synthesis of this MAP4 structure is accomplished according to the solid phase procedure of J.P. Tam, US Patent 5,580,563 and/or T. Toth, et al. US Patent 5,882,645 using a Fmoc-β-ala-Wang resin. After the deprotection Fmoc-β-ala from the resin, coupling is accomplished as described in Example 1. After the final amino acid residue is added, the Fmoc deprotection group was removed. The Wang resin is washed stepwise with DMF, methanol and DCN. The cleavage of the protecting group and the coupling reaction was monitored using the Kaiser Ninhydrin test. The purified MAP4 peptide produces satisfactory amino acid analysis.
MAP4 is then coupled with ePTFE as is described herein.

(b) Similarly, Example 1(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of RGD. (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 1(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR. (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 1(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of REDV. (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 1(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 1(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane.

Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 1(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 2

PREPARATION OF A MAP2

$(NH_2\text{-GTPGPQGIAGQRGVV})_2\text{-Lys-}\beta$ ala-COOH

(a) The MAP2 peptide, $(NH_2\text{-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val})_2\text{-Lys–}\beta\text{-Ala-COOH}$ was assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling was accomplished as described in Example 1, but with the specific amino acid sequence of the MAP4 peptide.

(b) Similarly, Example 2(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of RGD. (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 2(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR. (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 2(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of REDV. (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 2(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are

observed.

(f) Similarly, Example 2(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 2(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide).

Improved cell adhesion and cell proliferation are observed.

EXAMPLE 3

PREPARATION OF A MAP4

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_4\text{-}(Lys)_2\text{-}Lys\ (NH_2)\ -\ \beta\ ala\ -\ CONH_2$

(a) The MAP4 peptide, $(CH_3CO\text{-}Gly\text{-}Thr\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Gln\text{-}Gly\text{-}Gln\text{-}Arg\text{-}Gly\text{-}Val\text{-}Val)_4\text{-}(Lys)_2\text{-}Lys\text{-}\ (NH_2)\text{-}\ \beta\text{-}Ala\text{-}CO\ NH_2$ was assembled on a Fmoc-β-Ala Wang resin. A procedure similar to that of Example 1(a) was used. An additional lysine group was added to the Fmoc-β ala resin. The N-terminal group was protected by acetylation. The purified MAP4 produces satisfactory amino acid analysis. MAP 4 is then coupled with ePTFE.

(b) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated PTFE Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 3(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 4

PREPARATION OF A MAP2

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_2\text{-}(Lys)\text{-}Lys(NH_2)\text{-}\beta\text{-}ala\text{-}COOH$

(a) The MAP2 peptide, (CH_3CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val)$_4$-(Lys)-Lys(NH_2)-β-ala-COOH is assembled on a Fmoc-β-Ala Wang resin. A procedure similar to that of Example 3(a) is used. An additional lysine group is added to the Fmoc-β ala resin. The N-terminal group is protected by acetylation. The purified MAP4 produces satisfactory amino acid analysis. MAP 4 is then coupled with ePTFE.

(b) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy.

Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated PTFE Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 4(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 5

PREPARATION OF A MAP4

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_4\text{-}(Lys)_2\text{-}$ Lys (NH_2) - β ala - COOH

(a) A similar procedure as in Example 4 (a) was used in the preparation of $(CH_3CO\text{-}Gly\text{-}Thr\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Gln\text{-}Gly\text{-}Gln\text{-}Arg\text{-}Gly\text{-}Val\text{-}Val)_4\text{-}(Lys)_2\text{-}Lys(NH_2)\text{-}$ β-Ala-COOH. An additional lysine group was added to the Fmoc- β-ala resin. The purified MAP4 produces satisfactory amino acid analysis. The MAP was then coupled with ePTFE.

(b) Similarly, Example 5(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of RGD. (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 5(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR. (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 5(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of REDV. (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 5(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 5(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane.

Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 5(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 6

PREPARATION OF A MAP8

$(NH_2\text{-GTPGPQGIAGQRGVV})_8\text{-}(Lys)_4\text{-}(Lys)_2\text{- Lys - Lys - }\beta\text{ ala - COOH}$

(a) A procedure similar to that found in Example 1 (a) is used to prepare MAP peptide, $(NH_2\text{-GTPGPQGIAGQRGVV})_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-Lys-}\beta\text{-Ala - COOH}$ assembled on a Fmoc-β-Ala Wang resin. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP peptide produces satisfactory amino analyses.

A similar procedure as in Example 4 is used in the preparation of $(CH_3CO\text{-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Val-Val})_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-Lys}(NH_2)\text{-}\beta\text{-Ala-COOH}$. An additional lysine group is added to Fmoc-β-Ala Wang resin. The purified MAP8 produces satisfactory amino analysis. The MAP is then coupled with ePTFE.

(b) Similarly, Example 6(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of RGD.

(SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 6(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR. (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 6(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of REDV. (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 6(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 6(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 6(a) is repeated except that the substrate

ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 6(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 7

PREPARATION OF A MAP8

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}Lys(NH_2)\text{-}\beta\text{-}Ala\text{-}COOH$

(a) A similar procedure as in Example 4 is used in the preparation of $(CH_3CO\text{-}Gly\text{-}Thr\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Gln\text{-}Gly\text{-}Gln\text{-}Arg\text{-}Gly\text{-}Val\text{-}Val)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}Lys\text{-}Lys(NH_2)\text{-}\beta\text{-}Ala\text{-}COOH$. In this case, the MAP has eight arms. The purified MAP8 produces satisfactory amino analysis. MAP is then coupled with ePTFE as described herein.

(b) Similarly, Example 7(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of RGD. (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 7(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR. (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 7(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of REDV. (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 7(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of

SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 7(a) is repeated except that the cell-binding peptide in MAP is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

(g) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 7(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 7(a) is repeated except that the substrate

ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 8

PREPARATION OF

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}Lys\text{-}Lys\text{-}(NH_2)\text{-}\beta\text{-}Ala\text{-}CONH_2$

(a) The MAP8 peptide, $(CH_3CO\text{-}Gly\text{-}Thr\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Gln\text{-}Gly\text{-}Gln\text{-}Arg\text{-}Gly\text{-}Val\text{-}Val)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}$ Lys -Lys-$(NH_2)\text{-}\beta\text{-}Ala\text{-}COOH$ is assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1, but with the specific amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP8 produces satisfactory amino acid analysis. The MAP is then coupled with ePTFE as described herein.

(b) Similarly, Example 8(a) is repeated except that the cell binding peptide in MAP is replaced with a stochiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed when it is coupled with ePTFE.

(c) Similarly, Example 8(a) is repeated except that the cell binding peptide in MAP is replaced with a stochiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed when it is coupled with ePTFE.

(d) Similarly, Example 8(a) is repeated except that the cell binding peptide in MAP replaced with a stochiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed when it is coupled with polysulfone.

(e) Similarly, Example 8(a) is repeated except that the cell binding peptide in MAP is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed when

it is coupled with titanium alloy.

(f) Similarly, Example 8(a) is repeated except that the cell-binding peptide in MAP8 is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed when it is coupled with stainless steel.

(g) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated PTFE Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 8(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide).

Improved cell adhesion and cell proliferation are observed.

EXAMPLE 9 (A MAP 16)

PREPARATION OF

$(CH_3CO\text{-}GTPGPQGIAGQRGVV)_{16}\text{-}(Lys)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}Lys\text{-}Lys(NH_2)\text{-}\beta\text{-}Ala\text{-}COOH$

(a) The MAP16 peptide, $(CH_3CO\text{-}Gly\text{-}Thr\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Gln\text{-}Gly\text{-}Gln\text{-}Arg\text{-}Gly\text{-}Val\text{-}Val)_{16}\text{-}(Lys)_8\text{-}(Lys)_4\text{-}(Lys)_2\text{-}Lys\text{-}Lys(NH_2)\text{-}\beta\text{-}Ala\text{-}COOH$ is assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1, but with the specific amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP4 produces satisfactory amino acid analysis.

(b) Similarly, Example 9(a) is repeated except that the cell-binding peptide in MAP16 is replaced with a stochiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed when it is coupled with ePTFE.

(c) Similarly, Example 9(a) is repeated except that the cell-binding peptide in MAP16 is replaced with a stochiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed when it is coupled with ePTFE.

(d) Similarly, Example 9(a) is repeated except that the cell-binding peptide in MAP16 is replaced with a stochiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed when it is coupled with polysulfone.

(e) Similarly, Example 9(a) is repeated except that the cell-binding peptide in MAP16 is replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are

observed when it is coupled with titanium alloy.

(f) Similarly, Example 9(a) is repeated except that the cell-binding peptide in MAP 16 is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed when it is coupled with stainless steel.

(g) Similarly, Example 9(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 9(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 9A

PREPARATION OF - MAP8 - ANTI-INFLAMMATORY AGENT

$(Naproxen)_8$-$(Lys)_4$-$(Lys)_2$-Lys-Lys-(NH_2)-β-Ala-$CONH_2$

(a) The MAP8 peptide, $(Naproxen)_8$-$(Lys)_4$-$(Lys)_2$- Lys -Lys-(NH_2)-β-Ala-COOH is assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1(a), but with naproxen-amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP8 produces satisfactory amino acid analysis. The MAP is then coupled with ePTFE as described herein. This MAP-S when prepared as described in Example 1(g) to 1(o) exhibits enhanced anti-inflammatory properties.

EXAMPLE 9B

PREPARATION OF - MAP8 - GROWTH FACTOR

(Growth factor -VEGF)$_8$-$(Lys)_4$-$(Lys)_2$-Lys-Lys-(NH_2)-β-Ala-$CONH_2$

(a) The MAP8 peptide, (Growth Factor-VEGF)$_8$-$(Lys)_4$-$(Lys)_2$- Lys -Lys-(NH_2)-β-Ala-COOH is assembled on a Fmoc-β-Ala Wang resin. Following

deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1(a), but with the specific growth factor -VEGF amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP8 produces satisfactory amino acid analysis. The MAP is then coupled with ePTFE as described herein. The MAP-S when prepared as described in Example 1(g) to 1(o) exhibits enhanced growth factor properties.

EXAMPLE 9C

PREPARATION OF - MAP8 - ADHESION BARRIER

(Adhesion barrier-oligomer)$_8$-(Lys)$_4$-(Lys)$_2$-Lys-Lys-(NH_2)-β-Ala-$CONH_2$

(a) The MAP8 peptide, (Adhesion barrier-oligomer)$_8$-(Lys)$_4$-(Lys)$_2$- Lys - Lys-(NH_2)-β-Ala-COOH is assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1(a), but with the specific adhesion barrier oligomer such as SEPRAFILM as ligand of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin was washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions were also monitored using the Kaiser Ninhydrin test. The purified MAP8 produces satisfactory amino acid analysis. The MAP is then coupled with ePTFE as described herein. This MAP-S when prepared as described in Example 1(g) and 1(o) exhibits enhanced adhesion barrier properties.

EXAMPLE 10

MAP4 OF RGD & NAPROXEN

RGD-COOH as described herein is combined with an equimolar amount of naproxen (d-2-(6-methoxyl-2-naphlyl) propionic acid) and is combined under Merrifield solid state synthesis conditions with one equivalent of (NH_2Lys)$_4$-(Lys)$_2$-Lys-β-ala solid polymer. After the normal reaction times described herein,

the MAP is cleaved from the substrate in the conventional way and purified. A MAP4 having ligands about in the 50/50 ratio of about RGD/naproxen is obtained.

EXAMPLE 11

HUVEC CELLS

(a) In this example ePTFE films covalently coated with MAP4 peptide $(NH_2\text{-GTPGPQGIAGQRGVV})_4\text{-}(Lys)_2\text{-Lys-}\beta\text{-Ala-COOH}$ and linear peptide $NH_2\text{-GTPGPQGIAGQRGVV-CONH}_2$ (P-15) were evaluated for cell adhesion and proliferation using primary Human Umbilical Vein Endothelial Cells (HUVEC). Two identical experiments were conducted to make certain that the cell growth data were statistically reliable (Exp. A and Exp. B). ePTFE films with a thickness of 0.002" were obtained form Pall Corporation , Port Washington NY. Human Umbilical Vein Endothelial Cells (HUVEC) were purchased from Clonetics Corporation, East Rutherford NJ. Cells were initiated from P2 frozen stock to P3 and P3 cells were seeded on sample films at a density of 10,000 cells/cm^2 in the EBM medium. Standard cell initiation , seeding, incubation, trypsinization and counting procedures were used in the example (See for example R. Ian Freshney, Culture of Animal Cells, Wiley-Liss, 2000). 12-well plates were used in the cell culture and cells were counted after 24 hrs, 4 days, 7 days, 10 days 14 days and 17 days. After the peptide coating, samples were vigorously wasted with dionized water and ethanol to remove free (unbonded) peptide molecules on the surface.

Peptide coating density on coated ePTFE was evaluated using Amino Acid Analysis (AAA Service Lab, Boring Oregon). The results are listed in Table 8.

Table 8. Peptide Coating Density

Experiment No.	MAP4 (nMoles/cm^2)	P-15 (nMoles/cm^2)
11A	1.2	1.7
11B	1.3	1.3

Based on the theoretical calculation, if the surface area of the linear peptide molecule NH_2-GTPGPQGIAGQRGVV-$CONH_2$ (SEQ ID NO: 1) about 100Å (very conservative) then a single layer coverage of the linear peptide molecules would require about 0.3 nMoles/cm^2. The calculation considered the fact that the actual surface area of ePTFE is larger than the measured area because of the porous surface. Since the MAP peptide, (NH_2-Gly-The-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)$_4$-(Lys)$_2$-Lys-β-Ala-COOH, is about five times bigger than P-15, even less amount of the peptide is needed to form a single layer on ePTFE.

Uncoated ePTFE (ePTFE) and chemical activated (P+C) ePTFE were used as controls. For chemical activated samples, ePTFE films were only plasma treated and then chemically activated according to Methods. These samples did not have peptide coatings. Cell growth data were collected as triplicates from three individual wells. Cells were counted after 24 hours, 4 days, 7 days, 10 days, 14 days, and 17 days. Tables10 and 11 are the cell count results. Figures 1 and 2 are the cell growth curves. Cell counts after 24 hrs were used to calculate the average cell adhesion (See Table 9).

Table 9. Average Cell Adhesion after 24 Hours

Sample	Cell Adhesion (%)
ePTFE	8.3
P+C	16.6
P-15	16.9
MAP4	21.2

The average cell adhesion was 21.2% for MAP4 samples, about 17% for chemical activated and P-15 coated samples, and only 8.3% for ePTFE controls. The MAP peptide coated ePTFE had the largest increase in cell adhesion and cell proliferation over ePTFE control. The cell adhesion of the MAP peptide coated ePTFE after 24 hr was more than 250 percent better than that on ePTFE control. There were 350 percent more living cells on the MAP peptide coated ePTFE than that on ePTFE control after 17 days' incubation. The MAP peptide coated ePTFE was also more cell-promoting than the linear peptide coated ePTFE, about 22 percent more cells on the MAP peptide coated ePTFE. (Tables 10 and 11). Similar cell growth data were found for both the linear peptide coated and chemical-activated ePTFE samples. All cell count data were evaluated by the two-way statistical analysis of variance (Table 12).

The improved cell adhesion data by the MAP peptide coating on ePTFE provided the evidence that MAP peptides are more effective in cell-binding and cell-proliferation than liner peptides with similar cell adhesion domains. In this invention, it is demonstrated that the MAP peptide coating on ePTFE not only improved cell adhesion but also significantly enhanced cell proliferation over the linear peptide alone. The superior cell-promoting properties exhibited by the MAP peptide coating on ePTFE are due to its multiple cell adhesion domains within the MAP peptide molecule and its large size to form suitable orientation and conformation for approaching cells. Both cell adhesion and cell proliferation

were significantly improved on the MAP peptide coated ePTFE compared to ePTFE control and the linear peptide coated ePTFE. It appears that the linear peptide coating might have only made the surface of ePTFE more hydrophilic because the cell behaviors on the linear peptide coated samples were similar to that on chemically activated samples. The purpose of the chemical activation step is to introduce carboxylic groups onto the surface of ePTFE.

Table 10. Cell Density of Exp 11A*

Culture Time (Days)	1	4	7	10	14	17
ePTFE	748 ±111	482 ±42	1,882 ±191	2,721 ±133	5,384 ±174	4,632 ±383
P+C	1,616 ±111	2,219 ±84	4,656 ±151	8,009 ±585	11,917 ±364	15,390 ±301
P-15	1,664 ±145	2,243 ±125	4,077 ±292	7,575 ±301	10,469 ±743	14,956 ±221
MAP4	2,268 ±111	2,822 ±191	8,226 ±471	10,421 ±289	16,404 ±684	17,272 ±301

*The data represents the mean cell density (cell/cm^2) of three separate well counts and ± standard deviation.

Table 11. Cell Density of Exp 11B*

Culture Time (Days)	1	4	7	10	14	17
ePTFE	917 ±111	579 ±72	1,544 ±151	2,287 ±100	4,632 ±133	4,825 ±301
P+C	1,713 ±42	1,954 ±72	4,125 ±72	6,947 ±145	10,228 ±442	13,461 ±904
P-15	1,785 ±151	1,857 ±111	3,980 ±145	6,706 ±221	9,987 ±289	13,075 ±442
MAP4	1,978 ±42	2,147 ±42	4,921 ±332	9,263 ±434	14,232 ±585	16,645 ±663

*The data represents the mean cell density (cell/cm^2) of three separate well counts and ± standard deviation.

Table 12. Two-Way Statistical Analysis of Variance of Cell Count Data

Experiment	Comparison	*p*-value (set)	*p*-value (actual)	Significant Difference
11A	MAP4 and ePTFE	0.05	$P < 0.001$	Yes
	MAP4 and P-15	0.05	$P < 0.001$	Yes
	P-15 and P+C	0.05	$P < 0.001$	Yes
11B	MAP4 and ePTFE	0.05	$P < 0.001$	Yes
	MAP4 and P-15	0.05	$P < 0.001$	Yes
	P-15 and P+C	0.05	$P < 0.146$	No

(b) Similarly, Example 11(a) is repeated except that the cell-binding sequence in the MAP peptide is replaced with a stochiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 11(a) is repeated except that the cell-binding sequence in the MAP peptide is replaced with a stochiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 11(a) is repeated except that the cell-binding sequence in the MAP peptide is replaced with a stochiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesion and cell proliferation are observed.

(e) Similarly, Example 11(a) is repeated except that the cell-binding sequence in the MAP peptide is replaced with a stochiometrically effective amount of SIKVAV. Improved cell adhesive and cell proliferation are observed. replaced with a stochiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 11(a) is repeated except that the cell-binding

sequence in the MAP peptide is replaced with a stochiometrically effective amount of WQPPRAPI (SEQ ID NO: 6). Improved cell adhesion and cell proliferation are observed.

(g) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of hydroxyapatite. Improved cell adhesion and cell proliferation are observed.

(h) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of titanium alloy. Improved cell adhesion and cell proliferation are observed.

(i) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyarylsulfone. Improved cell adhesion and cell proliferation are observed.

(j) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyetherketone. Improved cell adhesion and cell proliferation are observed.

(k) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(l) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of polyurethane. Improved cell adhesion and cell proliferation are observed.

(m) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of surface treated stainless steel. Improved cell adhesion and cell proliferation are observed.

(n) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of HEMA. Improved cell adhesion and cell proliferation are observed.

(o) Similarly, Example 11(a) is repeated except that the substrate ePTFE is replaced with a structurally equivalent amount of poly(glycolide). Improved cell adhesion and cell proliferation are observed.

EXAMPLE 12

SMOOTH MUSCLE CELLS EVALUATION

In this example, Primary Human Smooth Muscle Cells (HSMC) were used to assess the effectiveness of peptide coated ePTFE film. All experimental procedures were similar to Example 1.

After incubating for 24 hours, about 87%, 72%, 68% and 33% of cells survived for MAP4 peptide coated, linear peptide coated, P+C control and ePTFE control, respectively. However, smooth muscle cells did not grow significantly after 4 days' incubation for all samples except ePTFE control. Number of cells on ePTFE control was more than doubled. Cells on other samples increased only about 30%. After 4 days' incubation, smooth muscle cells on MAP4 were only 50 percent more than that on ePTFE control (Table 13 and Figure 14). However, as discussed in Example 1, 400 percent more endothelial cells on the MAP peptide coated ePTFE than on ePTFE control during the same incubation period. This observation is very significant because the data indicate that this specific MAP peptide is more effective promoting HUVEC than HSMC. In other words, MAP peptides can be optimized for not only have the ability to promote cell growth, but also have the selectivity to attract specific cells. This is the exact required combination of surface properties that artificial implants need to have in order to be effectively integrated with the surrounding tissues, quickly forming a stable endothelial cell lining and slowing down the growth of smooth muscle cells. All experiment data were statistically significant (Table 14).

Table 13. Cell Density Experimental Results

Culture Time (Days)	1	2	3	4
ePTFE	7,888 ±205	11,316 ±558	15,263 ±744	17,105 ±1,116
P+C	16,355 ±614	23,158 ±1,116	24,079 ±1675	21,053 ±1,116
P-15	17,224 ±409	21,974 ±558	25,789 ±1,116	22,105 ±1,116
MAP4	20,842 ±409	24,079 ±930	26,711 ±558	27,237 ±558

Table 14. Two-Way Statistical Analysis of Variance of Cell Count Data

Comparison	p-value (set)	p-value (actual)	Significant Difference
MAP4 and ePTFE	0.05	P<0.001	Yes
MAP4 and P-15	0.05	P<0.001	Yes
P-15 and P+C	0.05	P<0.273	No

While only a few embodiments of the invention have been shown and described herein, it will become apparent to those skilled in the art that various modifications and changes can be made in the MAP structure and features of the compositions of matters, the pharmaceutical compositions, implants, methods of manufacture, or methods of therapy for in vivo adhesion, migration and proliferation of bioactive molecules and to provide anti-inflammatory and anti-thrombogenic properties without departing from the spirit and scope of the present invention. All such modifications and changes coming with the scope of the appended claims are intended to be carried out thereby.